IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

MERCK & CO., INC.,	:	
	:	
Plaintiff,	:	
	:	
v.	:	Civil Action No. 01-048-JJF
	:	(Consolidated)
TEVA PHARMACEUTICALS USA, INC.	:	
Defendant.	:	
	:	

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OPINION

August 28, 2003
Wilmington, Delaware.

Farnan, District Judge.

I. Procedural Background

Plaintiff, Merck & Co., Inc. ("Merck") is a Delaware corporation with its principal place of business in New Jersey. Defendant, Teva Pharmaceuticals USA, Inc. ("Teva") is a Delaware corporation with its principal place of business in Pennsylvania. Merck is the owner of the entire right, title and interest in United States Patent No. 5,994,329, entitled "Method for Inhibiting Bone Resorption" (the "'329 Patent"), which issued November 30, 1999, naming as inventors Anastasia G. Daifotis, Arthur C. Santora I, and John Yates. Merck filed the application for the '329 Patent on July 22, 1997. The '329 Patent is set to expire on August 14, 2018. (PTX 1).

Merck listed the '329 Patent in the Federal Drug Administration's ("FDA") publication "Approved Drug Products with Therapeutic Equivalence Evaluations" (the "Orange Book") in connection with its 70 mg and 35 mg dosage for alendronate sodium, which Merck markets under the name "Fosamax." On October 3, 2000, Teva filed a supplement to an existing Abbreviated New Drug Application ("ANDA") seeking FDA approval to market generic versions of Merck's 70 mg alendronate sodium product for weekly administration. Included with Teva's ANDA filing were "paragraph IV" certifications (21 U.S.C. § 355(j)(2)(A)(vii)(IV)) asserting that the Patents listed in the Orange Book, including the '329 Patent, are invalid, unenforceable or would not be infringed by

the commercial marketing of Teva's proposed product. Merck filed this action on January 21, 2001, alleging that Teva's filing of its supplement was an act of infringement under 35 U.S.C. § 271 (e)(2)(A). Thereafter, Merck listed U.S. Patent No. 6,225,294 (the "'294 Patent") in the Orange book and Teva filed a paragraph IV certification asserting that the '294 Patent is invalid, unenforceable or would not be infringed by the commercial marketing of Teva's proposed 70 mg alendronate sodium product. On October 4, 2001, Merck filed Civil Action No. 01-675-JJF, alleging that Teva's filing of its supplemental ANDA was an act of infringement of the '294 Patent under 35 U.S.C. § 271 (e)(2)(A).

Subsequently, Teva filed another supplement to its ANDA, seeking approval to market a generic version of Merck's 35 mg Fosamax product. The supplement also included a paragraph IV certification asserting that all the listed patents were invalid, unenforceable or would not be infringed by Teva's commercial marketing of its proposed product. On November 6, 2001, Merck filed Civil Action No. 01-728, alleging that the filing of Teva's supplement to the ANDA was an act of infringement under 35 U.S.C. § 271 (e)(2)(A). On January 14, 2002, the Court consolidated all three cases under Civil Action No. 01-048.

One of the listed patents against which Teva certified was U.S. Patent No. 4,621,077 ("the '077 Patent"), which had already been the subject of litigation between the parties in this Court

(Civil Action No. 00-035-JJF) in connection with Teva's application to market alendronate sodium for daily administration. The Court entered judgment in favor of Merck in that case on December 2, 2002, and an appeal from that judgment is now pending in the United States Court of Appeals for the Federal Circuit. (D.I. 123-1). The parties agreed that they will be bound in this case, with regard to issues concerning the '077 Patent, by a final decision in the prior litigation. (D.I. 128). Prior to trial Merck stipulated that the only claims at issue in this litigation are claims 23 and 37 of the '329 Patent and further stipulated that it would not allege an invention date for those claims prior to July 22, 1997. (D.I. 128).

Teva stipulated that if found valid and enforceable, claims 23 and 37 of the '329 Patent would be infringed by the commercial marketing of Teva's proposed 70 mg and 35 mg alendronate sodium products for weekly administration. (D.I. 109, Pretrial Order, Tab 1, ¶¶ 8-9). The issues of validity and enforceability of the '329 Patent were tried before the Court from March 4-7, 2003.

The Court has jurisdiction over the parties and the subject matter pursuant to 28 U.S.C. § 1338(a). Additionally, venue is appropriate under 28 U.S.C. § 1391(c) and § 1400(b). Neither jurisdiction nor venue are contested by the parties. This Opinion constitutes the Court's Findings of Fact and Conclusions of Law with respect to the issues tried before the Court.

II. The '329 Patent and Bone Biology In General

The '329 Patent discloses less-frequent-than daily administration of bisphosphonates (e.g., alendronate) to inhibit bone resorption. (D.I. 143 at 8). Claims 23 and 37, the only asserted claims, relate specifically to the treatment and prevention of osteoporosis by once-weekly administration of alendronate. Osteoporosis is related to processes that are imbalanced in bone, and therefore, the Court will discuss the background of bone biology as it relates to osteoporosis and the use of alendronate for treatment of the disease.

Bone is the tissue that provides mechanical support to the body. It is made up of a protein matrix, which is overlaid with mineral to give it hardness. (Russell[1] at 108-109; DTX 523 at 2). Two principal types of cells maintain bone: 1) osteoclasts, which break down bone, and 2) osteoblasts, which build new bone. Id. The process of bone destruction and rebuilding is known as "remodeling." In the bone remodeling process, osteoclasts attach to the bone surface, become activated, and erode away the bone material beneath them, leaving defects in the bone structure. The destruction of bone by osteoclasts is called bone "resorption." Osteoblasts then attach to the eroded surface of these defects, lay down new bone, and then become inactive. In the normal healthy adult the remodeling process is balanced. In

[1] The bench trial transcript is cited throughout the Opinion by a notation to the witness and the page number of the transcript.

other words, bone is destroyed and built at the same rate. (Russell at 109-110; DTX 523 at 3-4).

In osteoporosis, bone destruction and formation are no longer balanced and bone is destroyed faster than it is replaced. Therefore, osteoporosis can lead to bone that is thinner, weaker, more fragile and porous. (Russell at 110-115; DTX 523 at 7, 8). Osteoporosis is treated primarily by inhibiting bone resorption- thus restoring the balance between bone destruction and formation. Alendronate inhibits bone resorption by blocking the bone destroying effects of osteoclasts. (Russell at 116-117). A small portion of the ingested drug makes its way to and adheres to the bone surface, where it resides until it is taken up by osteoclasts. The alendronate then inhibits the osteoclasts from resorbing bone. (Russell at 121-122; DTX 523 at 10).

Paget's disease is also a common bone disease characterized by increased bone resorption. In Paget's disease, increased bone remodeling occurs in localized areas of the skeleton. If Paget's disease is not detected and treated early it can lead to an increase in bone size, fractures, and deformity. (Russell at 97). Like osteoporosis, Paget's disease is treated by inhibiting bone resorption with alendronate. (Russell at 125-126).

III. Teva's Motion in Limine to Preclude Merck From Relitigating the Factual Findings Underlying the Decision in Teva Pharmaceuticals Ltd. et al. v. Instituto Gentili Spa et al. (D.I. 113).

Teva filed a Motion in Limine to Preclude Merck from

Relitigating the Factual Findings Underlying the Decision in Teva Pharmaceuticals Ltd et al. Istituto Gentili Spa et al., (High Court of Justice, Chancery Division, Patents Court, January 21, 2003)). (D.I. 113). Accordingly, the Court will discuss the motion in limine before it delves into the issues of validity and enforceability of the '329 Patent.

Teva's principal defense in this case is that claims 23 and 37 are invalid because the claimed invention is anticipated or would have been obvious in view of the prior art. At the same time that the parties were litigating the validity of the '329 Patent in this Court, they were also involved in a case in the British High Court of Justice (the "High Court"). That case was a challenge by Teva and others to the validity of the European Patent No. 998,292 (the "'292 Patent"), which corresponds to the '329 Patent, and is based on the same provisional applications filed in July 1997. Teva, by its motion, contends that the '292 Patent covers the identical concept as the '329 Patent: the once-weekly dosing of alendronate sodium to treat osteoporosis, using seven times the normal daily dose.[2]

The High Court conducted a full trial on the merits from November 5-8, 2002, and heard further arguments from counsel on November 12-13, 2002. The trial involved live testimony from

[2] This claim is in the form of a "Swiss claim." Such claims are used in attempts to avoid restrictions on claiming methods of treatment, which are unpatentable in many countries.

Merck's expert Dr. Socrates Papapoulos, who is Merck's expert in this case. In addition, Merck offered the testimony of Dr. Yates, the principal inventor of the '329 Patent, who also testified in this case. On January 22, 2003, Justice Jacob of the High Court found that the claimed invention was invalid because it would have been obvious to a person skilled in the art, it claims a method of treatment, and is incapable of industrial application.

A. Applicable Legal Principles

Teva contends that the Court should adopt the High Court's factual findings concerning obviousness pursuant to the doctrine of collateral estoppel. Collateral estoppel is appropriate if: (1) the issue is identical to one decided in the first action; (2) the issue was actually litigated in the first action; (3) resolution of the issue was essential to a final judgment in the first action; and (4) plaintiff had a full and fair opportunity to litigate the issue in the first action. Micron Technology, Inc. v. Rambus, Inc., 189 F. Supp. 2d 201, 209 (D. Del. 2002) (citations omitted). Additionally, the doctrine of collateral estoppel applies in patent cases. See Blonder-Tongue Laboratories, Inc. v. University of Illinois Foundation, 402 U.S. 313 (1971).

B. Parties' Contentions

1. Teva's Contentions

By its motion, Teva contends that Merck had the identical motivation in litigating the British case as it does in the instant case: to discredit the Lunar News (a prior art reference) and Teva's reliance on its teachings. Moreover, Teva contends that Merck's barristers were afforded a full and fair opportunity to cross-examine all of Teva's witnesses and did so at length. Teva contends that the evidence was heard by Justice Jacob of the High Court, who is experienced in patents.

On January 22, 2003, Justice Jacob found the '292 Patent invalid and entered judgment against Merck. In its motion, Teva concedes that the legal standard may vary between Britain and the United States; nevertheless, Teva contends that regardless of the differences, if any, between the legal standards for determining validity, collateral estoppel should still apply to the resolution of the underlying factual issues. Specifically, Teva contends that all of the elements of collateral estoppel are met in this case with regard to the High Court's factual findings on obviousness.

First, Teva contends that collateral estoppel applies to fact findings of foreign courts. Teva argues that courts have recently recognized that parties who litigate in a foreign court should be bound by the results of that litigation to the extent that the requirements of the collateral estoppel doctrine are met. For example, Teva points to Vas-Cath, Inc. v. Mahurkar, 745

F. Supp. 517 (N.D. Ill. 1990), rev'd on other grounds, 935 F.3d 1555 (Fed. Cir. 1991), where the parties extensively litigated the issue of obviousness in Canada, and the district court held that the parties were bound by the fact-finding of the Canadian Court. Additionally, Teva points to Northlake Marketing & Supply, Inc. v. Glaverbel, S.A., 958 F. Supp. 373, 379 (N.D. Ill. 1997) ("Northlake I") and Northlake Marketing & Supply, Inc. v. Glaverbel, S.A., 986 F. Supp. 471, 475-76 (N.D. Ill. 1997) ("Northlake II"), where the parties had previously litigated the validity of a Belgian patent that corresponded to the United States patent in suit. The district court in those cases held that the Belgian Court's conclusions about the scope and content of prior art were binding on the parties in the United States litigation.

Further, Teva directs the Court to Oneac Corp. v. Raychem Corp., 20 F. Supp. 2d 1233, 1242-1243 (N.D. Ill. 1998), where a corresponding European patent was litigated in the High Court and the district court held that with respect to the United States patent, it would not give preclusive effect to questions of law or mixed questions of law and fact, but it would adopt the British Court's factual findings. Additionally, Teva points to Federal Circuit decisions that have declined to afford collateral estoppel effects to judgments in foreign cases, but distinguishes them on the basis that those decisions were predicated on what

the Federal Circuit views as different standards of patentability in other countries. See, e.g., Meditronic Inc. v. Daig Corp., 789 F.2d 903 (Fed. Cir. 1996)(declining to adopt German tribunal's determination that corresponding German patent was invalid in view of different legal standards); In re Duhlberg, 472 F.2d 1394 (C.C.P.A. 1973) (same).

Second, Teva contends that the issues were the same in the British litigation; the obviousness of administering alendronate sodium once a week at a dose of about seven times the daily dose. Further, Teva argues that the issue of the scope and content of the prior art are the same in both cases; whether the Lunar News publications taught the administration of alendronate sodium once a week, and whether the prior art taught that the dose should approximate seven times the daily dose. In addition, Teva argues that Merck's fear defense is an issue in both cases. Merck claims that persons skilled in the art would have rejected the Lunar News teachings because of the fear that patients would not tolerate the larger dose. Merck raised the issue in Britain, and after considering the evidence, the High Court concluded that the "fear defense fails". For example, the High Court found that the rare instances of esophageal side effects were attributed primarily to failure to follow the dosing instructions (D.I. 114, Ex. A, ¶ 65).

Third, Teva argues that the same issues were actually

litigated in the High Court. For instance, Teva contends, the parties fully aired all factual evidence, where both sides had qualified expert witnesses to explain the evidence to the Court. Further, Teva argues that all witnesses appeared live and were extensively cross-examined and after the trial both parties provided written submissions and appeared for extensive argument before Justice Jacob. As a result, Teva argues, Merck cannot contend that these issues were not litigated.

Fourth, Teva argues that the issues were determined by a valid and final judgment. Teva points out that the judgment of the High Court was the "Approved Judgement of that Court." It was issued on January 21, 2003 and reissued in corrected form January 22, 2003. Teva notes that Merck has appealed the judgment, but that fact does not imply that the judgment is not final for purposes of collateral estoppel. In fact, Teva argues that it is well settled that the pendency of an appeal does not diminish the preclusive effect of an appealed judgment. (D.I. 114 at 13) (quoting Rice v. Department of Treasury, 998 F.2d 997, 999 (3d Cir. 1993)).

Lastly, Teva contends that the resolution of obviousness was essential to the judgment in the High Court. Specifically, it contends that Justice Jacobs was required to and did evaluate and interpret the prior art provided by Merck's witnesses, and that, all findings on these issues were necessary to his final

judgment that the patent was invalid for obviousness. Based on this, Teva argues that the High Court's factual findings should be given preclusive effect.

2. Merck's Contentions

In response, Merck argues that there is no transnational collateral estoppel as to the validity of a United States Patent. First, Merck contends that Teva fails to point to a single Federal Circuit case where, a foreign court's judgment that the patent was invalid, or the factual underpinnings of such a judgment, was given collateral estoppel effect in a case litigating the validity of a United States Patent. In fact, Merck argues that the Federal Circuit and its predecessor court have rejected such attempts. For example in Meditronic Inc. v. Daig Corp., 789 F.2d 903 (Fed Cir. 1986), cert. denied, 107 S. Ct. 402 (1986), the Federal Circuit rejected the argument that it should adopt the conclusion of a German tribunal that a German counterpart was obvious and stated, "[t]his argument is specious. The patent laws of the United States are the laws governing a determination of obviousness/nonobviousness of a United States patent in a federal court." Id. at 907-908.

Additionally, Merck contends that the predecessor to the Federal Circuit came to the same conclusion in In re Duhlberg 472 F.2d 1394, 1398 (C.C.P.A. 1973) and In re Larsen, 292 F.2d 531, 533 (C.C.P.A. 1961), where in both cases, the court refused to

consider the actions of a foreign country's patent office with respect to the patentability of the subject matter before the court.

Further, Merck argues that district courts have refused to give collateral estoppel effect to a foreign court's judgment. For example, Merck points to Cuno, Inc. v. Pall Corp., 729 F. Supp. 234 (E.D.N.Y. 1989), where the High Court found the European counterpart of the United States patent at issue to be valid and infringed, and when the plaintiff sought to have the United States district court give collateral estoppel effect to certain factual findings, the court denied the request and stated that:

> Even if the court were to apply collateral estoppel to certain factual findings made by the British Court - as opposed to importing its legal conclusions wholesale–it is not clear that the trial time would be significantly shortened. Furthermore, the Federal Circuit's reluctance to give collateral estoppel effect to foreign judgments would seem to apply here to foreign findings of facts insofar as those findings involve mixed questions of fact and foreign law.

Id. at 238-239.

Moreover, Merck distinguishes the cases cited by Teva. First, in regard to the Oneac case, Merck points out that the court refused to give preclusive effect to questions of law or mixed questions of law and fact, and to the extent that certain factual findings were given collateral estoppel effect, it was because both parties to the suit agreed to be bound by those

factual determinations. Oneac Corp., 20 F. Supp. 2d at 1242-1243. Additionally, Merck points to the Vas-Cath case where the Northern District of Illinois adopted certain factual findings of a Canadian Court in regard to the validity of a patent, after parsing out the Canadian judgment, comparing the relative Canadian and United States' laws and making its own conclusions regarding the applicability of the factual determinations in the context of the United States' legal framework. Additionally, in the Northlake cases, Merck points out that the district court adopted only certain factual findings from a previous Belgian proceeding after careful review of those findings and contends that most importantly, the issues that were precluded limited the evidence that the patent challenger could rely on. See Northlake II, 986 F. Supp. 475-476; Northlake I, 958 F. Supp. at 379.

Next, Merck argues that the requirements for collateral estoppel have not been met. First, Merck contends that the High Court's factual findings regarding obviousness were not essential to the final judgment because the High Court found that the '292 was invalid based on three grounds: 1) invalid as a method of treatment; 2) incapable of industrial application; and 3) invalid as obvious- not obviousness alone.

Lastly, Merck argues that the facts and applicable legal standard is different. Specifically, Merck contends that in the United States obviousness is ultimately a question of law which

rests on the following factual inquiries: 1) the scope and content of prior art; 2) the level of ordinary skill in the art; 3) the differences between the claimed invention and the prior art; and 4) objective considerations of nonobviousness. See Advanced Display Systems, Inc. v. Kent State Univ., 212 F.3d 1272, 1284-85 (Fed. Cir. 2000). On the other hand, Merck argues, in Britain, the determination of obviousness is based on the following factual inquiries: 1) identifying the inventive concept embodied in the patent in suit; 2) assuming the mantle of the normally skilled but unimaginative addressee in the art at the priority date and impute to him what was, at that date, common general knowledge in the art; 3) identifying what, if any, differences exist between the matter cited as being made available to the public and the alleged invention; 4) determining whether, viewed without any knowledge of the alleged invention, those differences constitute steps which would have been obvious to the skilled man or whether they required any degree of invention. (D.I. 126 at 17) (citing Windsurfing International, Inc. v. Tabur Marine (Great Britain) Ltd., 1985 R.P.C. 59, 60-61 (1985 Ct. Of Appeal)). Merck contends that although these standards are similar, the United States Court is required to consider objective considerations of obviousness, while in Britain they are not. Accordingly, Merck contends that collateral estoppel is improper.

C. Discussion

As outlined above, the standards for determining obviousness in the United States and Britain are different. In fact, for purposes of this motion, Teva concedes that there may be differences in the legal standards for validity between the United States and Britain. Additionally, after reviewing the "factual findings" of the High Court, the Court finds that many of the principles are mixed questions of law and fact. The cases cited demonstrate that mixed questions of law and fact should not be adopted if there are two different legal standards, as in this case. See, e.g., Oneac Corp., 20 F. Supp. 2d at 1242-1243 (declining to adopt mixed questions of law and fact). Additionally, in Oneac the court only adopted factual findings from a foreign tribunal where the parties agreed to be bound by such factual findings. Id. at 1242-43. This is not the situation in the instant case because Merck opposes any adoption of the High Court's factual findings. Also, the Court finds that Merck has successfully distinguished the Northlake cases from the instant case, where in the Northlake cases the issues that were precluded limited the evidence that the patent challenger could rely on and the adopted factual findings did not go to the validity of the patent in suit.

The Court also concludes that all of the elements necessary for a finding of collateral estoppel are not present in this

case. Specifically, the High Court's factual findings relating to obviousness were not essential to the High Court's decision because that decision was based on three separate grounds as detailed above. The Third Circuit has stated that "if a judgment of a court of first instance is based on determinations of two issues, either of which standing independently would be sufficient to support the result, the judgment is not conclusive with respect to either issue standing alone." Arab African Int'l Bank v. Epstein, 958 F.2d 532, 535, (3d Cir. 1992) (quoting Restatement (Second) of Judgments § 27, cmt. i), rev'd in part on other grounds, 10 F.3d 168 (3d Cir. 1996). The Court concludes that based on this standard, the High Court's finding of obviousness cannot be said to be essential to the final determination.

There may be cases where "the balance tips in favor of preclusion because of the fullness with which the issue was litigated and decided in the first action." Masco Corp. v. United States, 303 F.3d 1329-1330 (Fed. Cir. 2002). However, the Court concludes that this is not such a case, especially in light of the fact that the Federal Circuit has cautioned courts against giving too much weight to foreign tribunals who are confronted with the same prior art. See Heidelberger Druckmaschinen AG v. Hantscho Comm. Prods., Inc., 21 F.3d 1068, 1072 (Fed. Cir. 1994) (recognizing that theories and laws of patentability differ from

country to country and stating that "[c]aution is required when applying the action of a foreign patent examiner to deciding whether the requirements of 35 U.S.C. § 103 are met under United States law, for international uniformity in theory and practice has not been achieved."). While the Court has reviewed Justice Jacob's factual findings in regard to obviousness, based on the aforementioned reasons, the Court declines to adopt them and will make independent findings of fact on the issue of validity. Accordingly, Teva's motion will be denied.

IV. Invalidity

Once issued a patent is presumed to be valid. See 35 U.S.C. § 282. The party challenging the patent bears the burden of proving by clear and convincing evidence that the patent is invalid. See Helifix Ltd. v. Blok-Lok Ltd., 208 F.3d 1339, 1346 (Fed. Cir. 2000). Clear and convincing evidence is evidence that places in the fact finder "an abiding conviction that the truth of [the] factual contentions are 'highly probable.'" Colorado v. New Mexico, 467 U.S. 310, 316 (1984).

Defendants contend that the '329 Patent is invalid and therefore cannot be infringed. Defendants argue invalidity on two grounds: anticipation by the July 1996 Lunar News reference under 35 U.S.C. § 102(e), and obviousness under 35 U.S.C. § 103. For the reasons set forth below, the Court concludes that the '329 Patent is valid.

A. Claim Construction

The first step in any invalidity analysis is claim construction which is an issue of law. SIBIA Neurosciences, Inc. v. Cadus Pharmaceutical Corp., 225 F.3d 1349, 1355 (Fed. Cir. 2000); Markman v. Westview Instruments, Inc., 52 F.3d 967, 970-71 (Fed. Cir. 1995) (en banc), aff'd, 517 U.S. 370 (1996). A claim term should be construed to mean "what one of ordinary skill in the art at the time of the invention would have understood the term to mean." E.g., Markman, 52 F.3d at 986. Further, when conducting a claim construction analysis, a district court should be cognizant of the fact that claims should be construed, if possible, to uphold their validity. In re Yamamoto, 740 F.2d 1569, 1571 & n.* (Fed. Cir. 1984) (citations omitted).

The starting point for a claim construction analysis is the claims themselves. Vitronics Corp. v. Conceptronic, Inc., 90 F.3d at 1582; see also Pitney Bowes, Inc. v. Hewlett Packard Co., 182 F.3d 1298, 1305 (Fed. Cir. 1999) (stating that "[t]he starting point for any claim construction must be the claims themselves."). Thereafter, the remainder of the intrinsic evidence should be examined beginning with the specification and concluding with the prosecution history. Vitronics, 90 F.3d at 1582 (outlining this order for examination in claim construction).

Generally, there is a strong presumption in favor of the

ordinary meaning of claim language as understood by those of ordinary skill in the art. Bell Atl. Network Servs., Inc. v, Covad Communications Group, Inc., 262 F.3d 1258, 1268 (Fed. Cir. 2001). However, it is well-settled that a patentee may act as his own lexicographer and use the specification to supply implicit or explicit meanings for claim terms. Bell Atl. Network Servs.,262 F.3d at 1268 (Fed. Cir. 2001); Vitronics Corp., 90 F.3d at 1582; Markman, 52 F.3d at 980 (noting that patentee is free to be his own lexicographer, but emphasizing that any special definitions given to words must be clearly set forth in patent). "[T]he patentee's lexicography must, appear 'with reasonable clarity, deliberateness, and precision' before it can affect the claim." Renishaw PLC v. Marposs Societa' per Azioni, 158 F.3d 1243, 1249 (Fed. Cir. 1998) (quoting In re Paulsen, 30 F.3d 1475, 1480 (Fed. Cir. 1994)).

If the meaning of a claim term is clear from the totality of the intrinsic evidence, than the claim may be construed. If, however, the meaning of a claim term is "genuinely ambiguous" after examining the intrinsic evidence, than a court may consult extrinsic evidence. Bell & Howell Document Mgmt. Prods. Co. v. Altek Sys., 132 F.3d 701, 706 (Fed. Cir. 1997).

Claim terms in claims 23 and 37 of the '329 Patent are disputed in this case. Accordingly, the Court will focus its discussion on these claims

In full, claim 23 of the '329 Patent provides, "[a] method according to claim 22 wherein said unit dosage of said bisphosphonate comprises about 70 mg of alendronate monosodium trihydrate on an alendronic acid active basis." (PTX 1, '329 Patent at col. 21, lines 24-27) (emphasis added).

In full, claim 37 of the '329 Patent provides, "[a] method according to claim 36 wherein said bisphosphonate unit dosage comprises about 35 mg of alendronate monosodium trihydrate, on an alendronic acid active basis." (PTX 1, '329 Patent at col. 22, lines 24-26) (emphasis added).

Teva contends that the term "about" in claims 23 and 37 should be construed according to its ordinary meaning of "approximately." (D.I. 147 at 3). Merck contends that the patentee in this case acted as his own lexicographer and set out the meaning of "about" in the specification where the specification explains that the term "about" accounts for the variability of weight of the active ingredient that would result from the use of different salts of alendronic acids. (D.I. 141 at 42). Thus, Merck contends that the phrase "about 70 mg" as used in claim 23 and "about 35 mg" as used in claim 37 means 70 and 35 mg respectively of the active ingredient on an alendronic acid active basis. Id. at 43. In other words, Merck contends that, regardless of the final weight of the actual active ingredient in the tablet, it contains the same number of

alendronate core molecules as 70/35 mg of alendronic acid.

In rebuttal, Teva contends that Merck's proffered construction makes no sense. Teva points out that according to Merck, the word "about" is used to account for the fact that different alendronate salts have different molecular weights, and that to deliver the same amount of physiologically active compound to the bone they must be delivered at slightly different dosage strengths. (D.I. 147 at 4). Teva contends that Merck's interpretation is nonsensical because the claim itself accounts for this phenomenon by directing that the compound be administered on the basis of a common denominator, i.e., "on an alendronic active basis." Id. In other words, Teva contends that the claims require that the amount "alendronate sodium trihydrate" be sufficient to deliver the same amount of active material as "about 70/35 mg" of alendronic acid. Id. As a result, Teva contends, the term "about" does not perform the function which Merck assigns to it, and must be in the claim for another purpose, that is, to have its ordinary meaning of "approximately."

After reviewing the claim terms and the specification, the Court concludes that the patentee explicitly and with reasonable clarity and precision defined the term "about 70 mg" in claim 23 and "about 35 mg" to mean the equivalent of 70/35 mg of alendronic acid when taking into account molecular weight

variances for its derivatives that carry accessories. Simply put, no matter what the final weight of the actual active ingredient in the tablet is, it contains the same number of alendronate core molecules as 70/35 mg of alendronic acid.

The relevant portion of the '329 Patent specification provides:

> Because of the mixed nomenclature currently in use by those or [sic] ordinary skill in the art, reference to a specific weight or percentage of bisphosphonate compound in the present invention is on an active weight basis unless otherwise indicated herein. For example the phrase "about 70 mg of bone resorption inhibiting bisphosphonate selected from the group consisting of alendronate, pharmaceutically acceptable salts thereof and mixtures thereof, on an alendronic acid weight basis" means that the amount of bisphosphonate compound selected is calculated based on 70 mg of alendronic acid.

PTX 1, the '329 Patent, col. 10, 65-col. 11, line 8. (emphasis added). The Court concludes that the specification clearly indicates that the terms "about 70 mg" and "about 35 mg" refer to the fact that depending on the derivative of the alendronic acid that could be used in the oral formulation, different weights will be needed in order to get the same effect as 70 or 35 mg of the seminal compound, alendronic acid. As Merck points out, the alendronate sodium in Fosamax includes an atom of sodium metal for each molecule of alendronate sodium. (D.I. 138 at 24). If a formulator was to select a different salt which includes a metal atom that is heavier than salt, e.g., a potassium or barium atom, the total amount of material in each tablet would have to

increase if the amount of alendronic acid were to remain the same. By conforming the weight of the alendronate derivative in the claim of the '329 Patent to the equivalent weight of the alendronic acid, a formulator can consistently know how many basic units (alendronic acid units) are to be used, even though the final total weight may be different. Examples 7 and 8 of the '329 Patent reinforce this conclusion. They provide for oral formulations "containing about 35 mg" and "about 70 mg" of alendronate "on an alendronic acid active basis." The claims at issue use the same phraseology and the ingredient tables in the examples are consistent with the premise that "about" accounts for the fact that alendronate derivatives have accessories that add to the weight of the molecules. Thus, in the examples "about 35 mg" turns out to be 45.68 mg of alendronate monosodium trihydrate and the "about 70 mg" turns out to be 91.35 mg of alendronate monosodium trihydrate. See PTX 1, the '329 Patent col. 19 lines 13-15, col. 19, lines 44-46, col. 19 lines 20-21, col. 19 lines 51-52.

Although the Court finds that Dr. Russell, is competent in the area of bisphosphonates, it does not find his opinion as to the definition of the phrases "about 70/35 mg" in the '329 Patent persuasive. During cross examination on this issue, Dr. Russell testified as follows:

> Q. Now is it true that when you deal with the claims in this case, the claims recite 70 and 35; correct? That

is 70 mg a week and 35?
A. The claims say about 70 and about . . . .
Q. And what does "about' mean to you?
A. Well about to me depends how precise a definition we want. But for purposes of how close the 40 and 80 are to about 35 and 70, I've given you my opinion on that, that for practical purposes, those would be the same, they would be indistinguishable in their effects, given everything else we know about the properties of these drugs.
Q. But the claim itself, what the claim really means, is 70, not 80; correct?
A. It says about 70 and about 35.
Q. Did you read the patent, Dr. Russell, the entire body of the patent?
A. Yes, I have.
Q. So in the patent, does it tell you what about 70 means?
A. There is a reference somewhere to about in the patent as I recall, but I'd need to be directed to where it was.
Q. Why don't you go to the first, in the patent, which is Defendant's Exhibit 1 and Plaintiff's Exhibit 1, at column 11, lines-about 1 through 9. It says here in the definitional context exactly what about 70 milligrams means; correct?
A. It- well, there's almost an intrinsic contradiction in this, because the definition here is talking about 70, and then referring to whatever salt form is used being referenced to the alendronic acid itself, yes.
Q. But in the patent it gives you a precise reference and says when we say about 70 milligrams of a bone resorption inhibiting bisphosphonate, what we mean is that amount of a bisphosphonate that will deliver an equivalent amount, the equivalent of 70 milligrams of alendronic acid; correct?
A. Yes. I have difficulty with this statement because the reason if it's that precise at 70, why does it use the phrase about?
Q. But they gave you that exact definition; correct?
A. It's a curious use of the English language.
Q. I understand, but it is what it says, and perhaps the person wanted to say if it's a certain salt one, you might use 71, and if it's a certain salt 2, you might use 73. Isn't that what's indicated in this?
A. Possibly.
Q. But that's what the definition says; right?
A. That is the definition as it's described in the

patent.

Russell at 337-339. (emphasis added). Although Dr. Russell opined that the explicit definition of the disputed claim terms in the specification was "a curious use of the English Language," he testified that Merck's proffered construction is the definition as it is described in the patent. The Court finds Dr. Russell's interpretation unpersuasive, especially in light of the fact that patentees may give special meanings to claim terms either explicitly or implicitly in patent specifications. Further, with regard to Teva's claim that there is no function to Merck's proffered construction, the Court finds this argument unpersuasive given the clear directive in the specification to construe the term "about 70/35 mg" to mean the equivalent of 70/35 mg of alendronic acid when taking into account molecular weight variances for its derivatives and the fact that depending on the derivative of alendronic acid used in the oral formulation, different weights will be needed in order to get the same effect as 70 or 35 mg of alendronic acid. See Bell Atl. Network Servs., 262 F.3d at 1268 (noting that the specification must express a clear intent to redefine a claim term). Accordingly, the Court will accept Merck's proffered construction and construe the disputed claim terms "about 70/35 mg" to mean the equivalent of 70/35 mg of alendronic acid when taking into account molecular weight variances for its derivatives that carry

accessories.

B. Anticipation

Anticipation is determined through a comparison of the claim language with a single prior art reference. See Wesley Jessen Corp. v. Bausch & Lomb, Inc., 209 F. Supp. 2d 348, 391 (D. Del 2002). In pertinent part, 35 U.S.C.§ 102(e)(2) provides:

> A person shall be entitled to a patent unless . . . (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that a patent shall not be deemed filed in the United States for the purposes of this subsection based on the filing of an international application filed under the treaty defined in section 351(a).

35 U.S.C. § 102(e)(2). Anticipation under 35 U.S.C. § 102(e) requires that every element of the claim be found either expressly or inherently "in a single prior art reference." In re Robertson, 169 F.3d 743, 745 (Fed. Cir. 1999). Thus, if the prior art reference does not expressly state an element of the claim, "that reference may still anticipate if that element is 'inherent' in its disclosure." Id. Inherency is established if the evidence makes "clear that the missing descriptive matter is necessarily present in the thing described in the reference and, and that it would be so recognized by persons of ordinary skill." Continental Can Co. v. Monsanto Co., 948 F.2d 1264, 1268 (Fed. Cir. 1991). Although inherency cannot be established through probabilities, recognition by a person of ordinary skill in the art before the critical date of the patent is not required to

show inherent anticipation. Schering Corp. v. Geneva Pharms., Inc., 2003 U.S. App. Lexis 15496 at *9-10 (Fed. Cir. August 1, 2003) (rejecting the contention that inherent anticipation requires recognition in the prior art before the critical date); In re Robertson, 169 F.3d at 745 (noting that inherent anticipation cannot be demonstrated through probabilities).

1. The Parties' Contentions

Teva contends that a July 1996 Lunar News article expressly anticipates claims 23 and 37 of the '329 Patent. Teva points out that since Merck has stipulated that it does not assert an invention date before July, 22, 1997, the July 1996 Lunar News is prior art under 35 U.S.C. § 102(a). (D.I. 143 at 19). Further, Teva points out that although it has the burden of proving invalidity by clear and convincing evidence, that burden is more easily met in this situation because Merck failed to provide the PTO with the July 1996 Lunar News.

Teva contends that the July 1996 Lunar News discloses every element of claims 23 and 37 of the '329 Patent. Teva points out that claim 23 defines a method of treating osteoporosis which comprises of oral administration of "about 70 mg" alendronate monosodium trihydrate, on an active alendronic acid basis, once-weekly. Similarly, Teva argues the July 1996 Lunar News discloses the same elements where it discusses the use of bisphosphonates, including alendronate, "in dealing with

osteoporosis," which means the treatment and prevention of osteoporosis. (D.I. 143 at 21; Russell at 137). Further, Teva contends that the July 1996 Lunar News also specifies that the alendronate therapy it is discussing includes "oral" alendronate therapy, and that the term "alendronate" refers to "Fosamax by Merck." Teva also contends that the active ingredient of Fosamax was well known to be alendronate monosodium trihydrate, and the dosage strength of Fosamax was known to be reported on an alendronic acid basis. (D.I. 143 at 21; DTX 394; Russell at 138-39). Teva also points out that the article specifies that the drug can be administered on a weekly basis at a dose of 80 mg where it states that, "...oral alendronate potentially could be given in a 40 or 80 mg dose once/week." (D.I. 143 at 21)(quoting DTX 418 at 23). Teva directs the Court to Dr. Russell's testimony where he opines that to a person skilled in the art, 80 mg of alendronate once per week is clinically indistinguishable from 70 mg once a week, and is therefore "about 70 mg." (D.I. 143 at 21; Russell at 138). Teva also contends that Merck itself viewed 80 mg and 70 mg as the same weekly dose. (D.I. 143 at 21; DTX 147 at MK0158265). Thus, Teva contends the July 1996 Lunar News Article discloses every element of claim 23: treatment of osteoporosis by the administration of about 70 mg monosodium trihydrate on an alendronic acid basis once-weekly. (D.I. 143 at 22).

Teva further contends that the July 1996 Lunar News anticipates claim 37 of the '329 Patent. Claim 37 claims a method for preventing osteoporosis in a human being comprising of orally administering about 35 mg of alendronate sodium on an alendronic acid basis as a unit dosage according to a continuous schedule having a dosage interval of once-weekly. (D.I. 143 at 22; DTX 1). Teva points out that the only difference between the two claims is that claim 23 is directed to "treatment" of osteoporosis with a 70 mg weekly dose, and claim 37 is directed to "prevention" with a 35 mg weekly dose. Teva reiterates the contention that the July 1996 Lunar News deals with both the treatment and prevention of osteoporosis and discloses the use of a 40 mg once-weekly oral dose. (D.I. 143 at 22). Teva again directs the Court to Dr. Russell's testimony where he testified that to a person skilled in the art, a 40 mg dose of alendronate once per week is clinically indistinguishable from 35 mg once per week and is therefore "about 35 mg." (D.I. 143 at 22; Russell at 140; DTX 147 at MKO158265). As a result, Teva contends that the July 1996 Lunar News discloses every element of claim 37: prevention of osteoporosis by oral administration of about 35 mg alendronate monosodium trihydrate on an alendronic acid basis once weekly. (D.I. 143 at 22).

Teva contends that Merck's "fear defense" is irrelevant to anticipation. First, Teva points out that claims 23 and 37 do

not require that once-weekly administration of alendronate meet any standard of safety or tolerability. (D.I. 143 at 23). Even if they did, Teva argues, such a requirement would not avoid anticipation because the property of tolerability is inherent in the method disclosed in prior art. Further, Teva argues that the concept of "teaching away" from an invention is inapplicable in an anticipation analysis, and therefore, the Court should not consider it. (D.I. 143 at 24). Based on this, Teva contends that claims 23 and 37 are anticipated by the July 1996 Lunar News, and are therefore, invalid.

In reply, Merck contends that the July 1996 Lunar News fails to anticipate claims 23 and 37 of the '329 Patent. Merck points out that the claims require the use of 70 or 35 mg of alendronate sodium on an alendronic acid active basis and even if one were to read the July 1996 Lunar News suggestion that "[e]ven alendronate potentially could be given in a 40 or 80 mg dose once/week" as referring to the amount on an alendronic acid active basis, 80 mg is not the same as 70 mg and 40 mg is not the same as 35 mg. Merck argues that the unambiguous weight requirement for alendronate in claims 23 and 37 is not met by the Lunar News' suggestion of 80 or 40 mg, and therefore, it fails to anticipate claims 23 and 37. (D.I. 138 at 27). Further, Merck argues that the July 1996 Lunar News is not enabling, and therefore, cannot anticipate. Specifically, Merck contends that in order for a

disclosure to be enabling it must allow one of skill in the art to practice the invention, and the July 1996 Lunar News falls short of this standard because it fails to address the expectation by physicians in the field during 1996-1997 that alendronate sodium at doses over 20 mg would not be well-tolerated in the prevention and treatment of osteoporosis. Merck points to Dr. Fennerty's testimony to establish that a knowledgeable gastroenterologist during the applicable period would have been "extraordinarily concerned" about suggesting 40 or 80 mg of alendronate to treat osteoporosis. (D.I. 138 at 28; Fennerty at 270-271).

Further, Merck argues that Dr. Papapoulos, Merck's expert with extensive bisphosphonate and clinical osteoporosis experience, corroborates this sentiment. (D.I. 138 at 28). Merck argues that given the state of the medical knowledge at the time, a physician would not administer those high dosages when managing osteoporosis, and as a result, the July 1996 Lunar News fails to anticipate claims 23 and 37 of the '329 Patent.

2. Whether the July 1996 Lunar News Anticipates the '329 Patent

After a review of the record evidence, the Court concludes that claims 23 and 37 of the '329 Patent are not anticipated under 35 U.S.C. § 102(e)(2). Specifically, the Court concludes

that Teva has failed to prove by clear and convincing evidence that the July 1996 Lunar News expressly or inherently discloses the dosage amounts for alendronate in claims 23 and 37. As a threshold matter and contrary to Teva's contentions, it has to prove invalidity by clear and convincing evidence. See American Hoist & Derrick Co. v. Sowa & Sons, Inc., 725 F.2d 1350, 1360 (Fed. Cir. 1984)(citations omitted) (stating that when a challenger produces prior art not before the PTO "the standard of proof does not change; it must be by clear and convincing evidence or its equivalent.") With this standard in mind, the Court will consider the parties' contentions with regard to anticipation.

The Lunar corporation was a manufacturer of bone densitometry equipment, which is a diagnostic tool for osteoporosis. (Russell at 129). The Lunar News was a quarterly newsletter distributed by the Lunar Corporation to its customers. (Mazess Dep. at 55-56; Russell at 129). It was authored by Dr. Richard Mazess[1], the former President of the Lunar Corporation. The July 1996 edition[2] contained a section entitled, "Update

[1] Dr. Mazess does not possess an MD, has no formal training in pharmacology, and obtained his bachelors degree and Ph.D. in anthropology. (Mazess Dep at 30-32).

[2] The Court understands that Teva is not contending that the April 1997 edition of the Lunar News anticipates the '329 Patent. See D.I. 143, Opening Brief at 19-24(failing to assert that the April 1997 Lunar News anticipates claims 23 and 37 of the '329 Patent). However, even if Teva made this assertion, the Court concludes that the April 1997 Lunar News did not anticipate claims 23 and 37 because it does not suggest any dosage amounts

Bisphosphonate." (PTX 29 at 23). The section discusses bisphosphonates as a treatment for osteoporosis. Id. Specifically, in reference to the use of alendronate for treatment of osteoporosis, it states that "[s]ome United States physicians are reluctant to treat because of: a) side effects; b) difficulty of dosing; and (c) high costs ($700/year). (PTX 19 at 23). To address the difficulty of dosing and high costs the article suggests:

> The difficulties with oral bisphosphonates may favor their episodic (once/week) or cyclical (one week each month)administration. Even oral alendronate potentially could be given in a 40 or 80 mg dose once/week to avoid dosing problems and reduce costs.

PTX 29 at 23. Teva contends that the July 1996 Lunar News article discloses all of the elements in claim 23 of the '329 Patent. Specifically, Teva argues that the July 1996 Lunar News discloses the following elements: 1) A method of treating osteoporosis in a human; 2) orally administering; 3) about 70 mg; 4) of alendronate monosodium trihydrate; 5) on an alendronic acid active basis; 6) as a unit dosage; and 7) according to a continuous schedule having a dosing interval once-weekly. (D.I. 143 at 23). Merck asserts that the July 1996 Lunar News article does not anticipate claim 23 because it fails to reference 70 mg of alendronate sodium on an alendronic acid active basis as

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in connection with its discussion of once-weekly dosing of alendronate. (DTX 417). Thus, it does not disclose all of the elements of claims 23 and 37, namely "about 35/70 mg" of alendronate, and therefore, cannot anticipate the claims either expressly or inherently.

required by claim 23. (D.I. 141 at 44).

After reviewing the July 1996 Lunar News in light of the '329 Patent, and the Court's construction of the claim terms, the Court is not persuaded that Teva has demonstrated by clear and convincing evidence that claims 23 and 37 of the '329 Patent are anticipated by the July 1996 Lunar News. The July 1996 Lunar News fails to reference 70 mg of alendronate sodium on an alendronic acid basis as required by the claim. Instead it references an 80 mg dose of oral alendronate. Thus, it does not expressly disclose "about 70 mg" of alendronate sodium "on an alendronic acid basis." Likewise, the Court is not persuaded that Teva has demonstrated inherency. Although Dr. Russell testified that 80 mg and "about 70 mg" are the same for all practical purposes because they have the same effect on patients, he did not testify that this element was "necessarily present" in the July 1996 Lunar News reference or that its disclosure was sufficient to show that this element was the natural result flowing from the operation as taught. In fact, in the Court's view, Dr. Russell's testimony was insufficient on this issue, and was, at best, conclusory. For example, although Dr. Russell testified that 80 mg and 70 mg are the same for all practical purposes because they would have the same effect, the Court recognizes that in rendering his opinion Dr. Russell did not take into account the Court's construction of the term "about 70 mg".

(Russell at 137-139). Further, the Court notes that Dr. Russell provided no evidence to support his conclusion that 70 and 80 mg were equivalent. In fact, Dr. Papapoulos testified on cross-examination that one would need to test the 80 and 70 mg doses before concluding with any certainty that they are the same and the regulations regarding the filing of an ANDA recognize that any change in the dosage of a drug would require additional data. (Papapoulos at 676-678; 21 U.S.C. § 355 (j)(2); 21 C.F.R. § 314.93). Dr. Russell, provided no such data. Based on this, the Court concludes that Teva has failed to demonstrate that the July 1996 Lunar News inherently or expressly disclosed the element of "about 70 mg" of alendronate sodium "on an alendronic acid active basis" as required by claim 23 of the '329 Patent.

Similarly, the Court concludes that the July 1996 Lunar News fails to disclose "about 35 mg" as required by claim 37 of the '329 Patent. Specifically, the July 1996 Lunar News fails to reference "35 mg" of alendronate sodium "on an alendronic acid active basis" as required by the claim. Although it references "40 mg", in light of the Court's claim construction of "about 35 mg" to mean the equivalent of 35 mg of alendronic acid when taking into account molecular weight variances for its derivatives that carry accessories, the Court concludes that the July 1996 Lunar News reference does not expressly disclose "about 35 mg" as required by claim 37. Likewise, the Court concludes

that Teva's inherency argument as to claim 37 must also fail. Dr. Russell testified that a 40 mg dose is about the same as a 35 mg for all practical purposes. (Russell art 140-141). However, the Court finds Dr. Russell's opinion on this issue to be conclusory because he provides no evidence, statistical tests or data to support this assertion. Further, Dr. Russell did not testify that this element was "necessarily present" in the July 1996 Lunar News reference or that its disclosure was sufficient to show that this element was the natural result flowing from the operation as taught. Based on this, the Court finds that the evidence is insufficient to show that each element of claims 23 and 37 of the '329 Patent were present in the prior art reference expressly or inherently. Accordingly, the Court concludes that Teva has failed to establish by clear and convincing evidence that the '329 Patent was anticipated by the July 1996 Lunar News. Because the Court concludes that claims 23 and 37 of the '329 Patent were not anticipated by the July 1996 Lunar News, the Court will not address the parties' contentions concerning enablement of the prior art.

C. Obviousness

Teva contends that the '329 Patent is invalid, under 35 U.S.C. § 103, as obvious. In pertinent part, 35 U.S.C. § 103 provides that a patent may not be obtained "if the differences between the subject matter sought to be patented and prior art

are such that the subject matter as a whole would have been obvious to a person having ordinary skill in the art . . .” 35 U.S.C. § 103. The obviousness determination is a question of law which is based on several underlying factual inquiries. See Richardson-Vicks Inc. v. UpJohn Co., 122 F.3d 1476, 1479 (Fed. Cir. 1997). The underlying factual inquiries require consideration of the four “Graham” factors which are: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the pertinent art; and (4) any secondary considerations of nonobviousness such as commercial success, long felt but unsolved need, failure of others, and acquiescence of others in the industry that the patent is valid. See Graham v. John Deere Co. of Kansas City, 383 U.S. 1, 17-18 (Fed. Cir. 1996). Additionally, as with anticipation, the burden of demonstrating obviousness is with the challenger and invalidity must be proven by clear and convincing evidence. C.R. Bard, Inc. v. M3 Systems, 157 F.3d 1340, 1351 (Fed. Cir. 1998).

1. The Parties’ Contentions

Teva contends that the ‘329 Patent is invalid as obvious because both the April 1997 and July 1996 editions of Lunar News explicitly disclose the weekly administration of alendronate for osteoporosis and a person skilled in the art would have understood in July 1997 that the weekly dose for treatment and

prevention of osteoporosis should be "about 70 mg" and "about 35 mg" respectively, and that these doses are explicitly set out in the July 1996 Lunar News. Teva argues that not only did the Lunar News disclose the concept of once-weekly dosing and provide the appropriate dose, a person of ordinary skill would have predicted the Lunar News teaching to be effective. (D.I. 143 at 26).

Further, Teva contends that there was a motivation to employ once-weekly dosing because of the inconvenience of the dosing regimen which consisted of taking the tablet before eating, remaining upright for a half an hour and taking the tablet with a full glass of water. Id. at 27. Teva points out that the April 1997 and July 1996 editions of Lunar News explicitly stated the motivation to administer alendronate weekly; to improve patient convenience and compliance with the dosing instructions. Id. Thus, Teva argues that the prior art that claimed the invention also disclosed the motivation to make it. Id.

Teva contends that a person of skill in the art would not have been deterred from once-weekly dosing because of the fear of increased gastrointestinal side effects. Id. As to this point Teva argues that the early reports of esophagitis would not have deterred a person of skill in the art from once-weekly dosing because the early reports showed that these events were rare, occurring in one out of every ten thousand patients taking 10 mg of alendronate daily, and that these effects were for the most

part reversible with proper treatment. Id. at 28; Markowitz at 436-37; 451. Teva also points out that in March 1996, five months after the launch of 10 mg daily alendronate tablet, ten million patients had been prescribed the tablet and fifty cases of severe esophagitis had been reported to Merck, and Merck took no action until it learned that a letter written by a well-known bone-specialist discussing two such cases was circulating within the Mayo Clinic Health System. (D.I. 143 at 29; Hirsch Dep.at 54-56). When it finally took action, Teva argues, Merck's investigation concluded that the pill esophagitis cases were caused primarily by the failure of patients to adhere to the dosing instructions. (D.I. 143 at 29; Markowitz at 442; Hirsch Dep. at 66; 82-84).

Teva also points out that in March 1996, Merck disseminated a "Dear Doctor" letter, informing physicians about the infrequent cases of esophagitis, stating that in a "large majority" of cases patients appeared to have not complied with the dosing instructions, and advocating "strict compliance" with those instructions. (D.I. 143 at 30; DTX 34). Merck later reported on the severe esophagitis cases in the October 1996 De Groen et al.[3] article in the New England Journal of Medicine. (PTX 91). The De Groen paper reported that 51 patients experienced adverse effects classified as "serious" or "severe" out of the 470,000

[3] De Groen et al., The New England Journal of Medicine, 1996 (PTX 91).

patients worldwide who had received prescriptions for alendronate to treat osteoporosis up to that time. (D.I. 143 at 30). Teva directs the Court to its gastroenterology expert, Dr. David Markowitz, who testified that the extremely low incidence of these effects, and the description of the cases, led gastroenterologists to conclude at the time that the likely cause of the problem was "pill esophagitis." (D.I. 143 at 30; Markowitz 435, 438). Teva argues that the evidence presented at trial leads to the conclusion that once-weekly administration would have been expected to decrease the incidence of severe esophagitis cases because it would: 1) improve patient compliance with the dosing instructions (Russell at 195-96; Markowitz at 485-86; Fennerty at 311); and 2) decrease the frequency of administration, thereby decreasing the chances of the tablet "sticking" in the esophagus (Russell at 196-197; Markowitz at 443).

Teva also asserts that the evidence presented at trial does not support a dose-response relationship between alendronate and gastrointestinal effects that would have deterred a person of ordinary skill in the art from once-weekly dosing. (D.I. 143 at 32). For example, Teva argues that the results of the Chestnut[4] study related to daily and not weekly dosing and demonstrated that 90% of postmenopausal women with osteoporosis tolerated the

[4] Chestnut et al., The American Journal of Medicine, 1995, (PTX 69).

40 mg daily dose. Id. at 34. Also, Teva contends that Dr. Fennerty's testimony regarding a dose-related relationship was discredited by Merck's pre-litigation behavior and directs the Court to the testimony of Dr. Markowitz who testified that his contemporaneous investigations indicated that severe events were extremely rare with alendronate and that overall the drug was well tolerated. Id. at 35.

In addition, Teva contends that before this litigation, Merck admitted that prior art data available in July 1997 from Paget's patients showed that once weekly dosing would be well-tolerated. For example, Teva directs the Court to a May 1997 "Tactical PAC" review seeking management approval to go forward with the once-weekly dosing program where it stated that "the 40 and 80 mg doses were well-tolerated even when given on a daily basis." (D.I. 143 at 39, DTX 147 at MK0158265). Further, Teva points out that Merck, in a formal submission to the FDA maintained that data from Paget's disease provided an expectation that once-weekly doses would be well tolerated. (D.I. 143 at 39; DTX 192 at 17).

Teva also argues that a person of skill in the art would not have been deterred from once-weekly dosing because of the alleged dose-related effects of prior art bisphosphonates, because the magnitude of data available on alendronate in treating osteoporosis and Paget's disease made reference to other

bisphosphonates unnecessary. (D.I. 143 at 41). Teva also points out that Merck's Physician Survey conducted in 1997 indicated that physicians perceived that larger less-frequent doses would result in "less-GI upset." (D.I. 143 at 43; DTX 244 at MK0174861).

Teva also contends that the '329 invention did not provide unexpected results because the prior art disclosed its principal advantage; convenience and compliance. (D.I. 143 at 44). Additionally, Teva contends that Merck did not carry its burden of demonstrating commercial success because it was required to show that the once-weekly product contributed to the incremental success beyond the daily product and that Merck's expert, Dr. Vellturo failed to demonstrate any connection between the patented invention and Merck's sales of once-weekly Fosamax. Specifically, Teva contends that Dr. Vellturo did not opine that the two were connected but merely asserted that "commercial success could be at least in part, significant part, attributable to the Daifotis patients." D.I. 143 at 48; Vellturo at 715. Further, Teva suggests that Dr. Vellturo's analysis is flawed because of his emphasis on sales and prescriptions as the only indicia of success without considering any other market factors such as the increased awareness about osteoporosis and the effect of the increasing number of Americans over the age of sixty, like its own expert, economist, Dr. Richard Rozek took into account.

(D.I. 143 at 48). Additionally, with regard to commercial success, Teva contends that Merck ignored its own successful marketing efforts such as its heavy promotional expenditures during the applicable period when examining the commercial success of the once-weekly dose of alendronate. (D.I. 143 at 51). Finally, Teva argues that Dr. Vellturo's diffusion model is flawed because a diffusion model in not particularly useful as a forecasting devise, and therefore, its use in this context is inappropriate and alternatively argues that Dr. Vellturo's use of the model is incorrect. (D.I. 143 at 54).

In response, Merck contends that the once-weekly high dose regimen of the '329 Patent was not obvious to a skilled practitioner in 1997 because without hindsight, the overwhelming knowledge in the field was that high oral unit doses would not be safe and tolerable for osteoporotic women. Merck points out that Dr. Russell, Teva's expert, acknowledged that a person of ordinary skill "would be familiar with publications in the field and the technical background in this field of bisphosphonates and osteoporosis." (Russell at 144). Thus, according to Dr. Russell's interpretation of one of ordinary skill, Merck argues, a skilled practitioner would know that: 1) etidronate and clodronate caused gastrointestinal side effects at high doses; 2) pamidronate caused dose-related gastrointestinal side effects that even led to the discontinuation of its development as an

oral medication; 3) alendronate caused dose-related gastrointestinal side-effects; and 4) alendronate sodium, even though proven to be safe and tolerable at 10 and 5 mg doses, could still potentially cause severe upper gastrointestinal injuries. (D.I. 145 at 10-11) (citations omitted). Merck contends that the overwhelming knowledge, laid out by contemporaneous publications in respected peer-reviewed medical journals establishes that the pre-invention expectation by those skilled in the art was that one could not use alendronate sodium at unit doses higher than 20 mg for the management of osteoporosis. Id. at 11.

Further, Merck asserts that Teva's "spin" on the Chestnut study is flawed. Specifically, Merck points out that in the Chestnut study only one out of sixty two women (1.6%) withdrew from the 10 and 5 mg doses, but seven out of sixty three women (11.1 %) withdrew from the 40 mg alendronate treatment. Id.; PTX 69 at 150; Markowitz at 479-482; Fennerty at 266. Moreover, contrary to Teva's assertion, Merck points out that it informed the FDA that the Chestnut Study had led it to "limit the maximum dose to 20 mg in subsequent osteoporosis treatment studies." (D.I. 145 at 15; PTX 202 at MK250180; PFF 66). Additionally, Merck asserts that as Dr. Papapoulos testified, a skilled practitioner at the time knew that in actual clinical practice 10 to 12 percent of patients discontinued 10 mg Fosamax treatment

because of gastrointestinal side effects. (D.I. 145 at 12; Papapoulos at 651-652). Thus, Merck argues that any reasonable clinician, viewing this data could compare these ratios and would expect the discontinuation rate for osteoporotic women in actual practice, outside the confines of a controlled clinical environment, to have been unacceptably high at a 40 mg dose. Merck asserts that Teva failed to consider that clinical studies are different than daily practice and that discontinuations are far less common in the context of a clinical study. (D.I. 145 at 12; PFF 60; Fennerty at 262-64).

In reference to Teva's reliance on internal and FDA submitted documents, Merck contends that these publications as presented by Teva were taken out of context, and therefore, do not bolster Teva's argument with regard to obviousness. Merck argues that Teva improperly relied on these documents because these documents reflect the inventors' rationales to overcome the skepticism about high unit doses and the inventors' insights about their own invention. In regard to extrapolating results from the Paget's disease experience to doses for osteoporosis, Merck points out that Professor Fleish's book, which Dr. Russell later edited, reflected the thinking in the art that the tolerability for alendronate sodium appeared to be higher for the Pagetic disease population than the osteoporosis population. (D.I. 145 at 15).

Merck also contends that it has never disputed that it was known that once-weekly dosing would be efficacious in providing the alendronate sodium needed to inhibit bone resorption, but notes that it was the safety concern about high oral doses (higher than 20 mg) that obscured the advantageous once-weekly invention for the management of osteoporosis. (D.I. 145 at 15). Further, Merck points out that it did not rely on the case reports such as De Groen as evidence of a dose-response, rather, Merck claims, the case reports simply raised the awareness of physicians that alendronate sodium was a potentially dangerous agent and that Teva's expert, Dr. Markowitz admitted that the case reports were clinically significant. (D.I. 145 at 18; Markowitz at 468). Merck also rebuts the contention that it took no action in response to the case reports and points out that it promptly obtained data about each case, constructed a data base and organized a meeting with Dr. De Groen and other consultants by March 1996. Then, on March 15, 1996 Merck sent out a "Dear Doctor" letter informing physicians about the potential upper gastrointestinal injuries and emphasizing the importance of following directions in order to minimize them. Merck also undertook internal studies to understand the problem, including dog studies. (D.I. 145 at 19 ; PTX 67; PFF 88).

In reference to Dr. Fennerty's testimony, Merck contends

that Teva mischaracterized his testimony regarding the Blank[5] article. Merck asserts that the Blank study provided a glimpse as to what happens when the use of aminobisphosphonates is combined with Non-Steroidal Anti-Flammatory Drugs ("NSAIDs") such as aspirin and ibubrofen. This study was published during February of 1997 in the peer reviewed Digestive Diseases and Sciences, and it showed clear dose-related upper gastrointestinal injuries from alendronate sodium when it was combined with the NSAID indomethacin in a rat model. (D.I. 145 at 20; PTX 104 at 284 fig. 3). Merck contends that Dr. Fennerty observed that when placed in the mosaic of prior art showing the dose dependent injuries from bisphosphonates, the Blank study was important to gastroenterologists, and he never retreated from this position. (Fennerty at 270, 292-94). Additionally, Merck points out that Teva itself stated to the PTO in 2000, in an attempt to gain the issuance of claims for a delayed gastric release alendronate formulation, that bisphosphonates as a class exhibit side effects that "consist of irritation of the upper gastrointestinal mucosa ... with the potential for this irritation leading to more serious conditions." (PTX 301, U.S. Patent No. 6,476,006 ("the '006 Patent") at col.3, lines 25-25). Merck contends that Teva also told the PTO that the "larger" once weekly doses have "the potential of exacerbating the upper GI side effects of the drug."

[5] Blank et al., Digestive Diseases and Sciences, 1997 (PTX 106).

D.I. 145 at 21 (quoting the '006 Patent at col. 3, lines 12-14).

Merck argues that Teva's reliance on the 1997 Physicians Survey is misplaced because it did not address the use of higher doses. Specifically, Merck points out that at issue is the invention of administering seven-fold the daily dose of alendronate sodium once a week, and in the survey, a twice-weekly dosing schedule was inquired about along with other choices that included placing alendronate sodium in diet colas and cranberry juice. (D.I. 145 at 22; DTX 244 at 174866). Merck points out that the invention of the '329 Patent does not lie solely in the less frequent dosing, but in the fact that an entire weekly complement of daily doses could be administered as a single unit dose and that the marketing survey inquired about twice weekly dosing without any mention of increasing the dose. Therefore, Merck argues that it does not bear any relevance to the invention of once-weekly dosing at sevenfold the daily dose. (D.I. 145 at 22).

In regard to secondary considerations, Merck contends that contrary to Teva's assertion that commercial success is irrelevant in the obviousness inquiry because Merck was the only entity allowed to market alendronate sodium tablets, its direct competitors, including Procter & Gamble, had an incentive to develop an improved dosage form. (D.I. 145 at 23). Further, in reference to commercial success, Merck contends that the

increased sales for the Fosamax franchise upon the launch of the once-weekly dosing regimen is dramatic regardless of which way it is viewed. (D.I. 145 at 25). Specifically, Merck points out that the Fosamax franchise sales followed a constant increase trend from 1996 until the introduction of once-weekly Fosamax in 2000, where if the trend established before the once-weekly dose was introduced had continued, an increase of 18.9% over the prior year would have resulted. However, after the once-weekly dosing was introduced, a dramatic increase of 42.5% was realized. (D.I. 145 at 26; PTX 166; Vellturo at 718-720). Additionally, Merck contends that Teva's attempt to discredit Dr. Vellturo's diffusion model was unsuccessful. Merck argues that, in any event, Dr. Vellturo testified that his opinion regarding the commercial success of the '329 Patent was not based on model, but on a fundamental shift in the constant trends he observed regarding the Fosamax franchise's sales increases, market share, prescription volume and on an evaluation of the market share and prescription volume data for the osteoporosis market as a whole, and that the diffusion model only confirmed the opinion he formed based on the aforementioned factors. (D.I. 145 at 26; Vellturo at 718-728, 735, 755-757). Finally, Merck notes that Dr. Rozek, Teva's expert on obviousness, provided no ultimate conclusion about the commercial success of the once-weekly dosing of Fosamax or any of the factors he believed Dr. Vellturo should have considered. (D.I. 145 at 26).

2. Whether the '329 Patent Was Obvious in View of the Prior Art

After reviewing the relevant prior art in light of the evidence and the factors related to the obviousness inquiry, the Court concludes that Teva has failed to establish by clear and convincing evidence that the '329 Patent was obvious in light of the prior art references. The Court in its obviousness analysis must be cognizant of "hindsight syndrome." In re Warner Kotzab, 217 F.3d 1365, 1369-1370 (Fed. Cir. 2000). The Federal Circuit has instructed that, "the best defense against the subtle but powerful attraction of a hindsight-based obviousness analysis is rigorous application of the requirement for a showing of the teaching or motivation to combine prior art references." In re Gartside, 203 F.3d 1305, 1329 (Fed. Cir. 2000). Therefore, in order to establish obviousness from a combination of elements disclosed in prior art, "there must be some motivation, suggestion or teaching of the desirability of making the specific combination that was made by the applicant." Kotzab, 217 F.3d at 1370. With this standard in mind, the Court will discuss the relevant factors of the obviousness inquiry as they relate to the '329 Patent.

i. Level of One Skilled in the Art

For the purposes of the obviousness inquiry, the Court finds that at the time of the filing of the '329 Patent, a person of

ordinary skill in the art was an individual who would have an M.D. and/or Ph.D. and was working in the field of and doing research on osteoporosis. Such a person would be familiar with the publications and technical literature and background in the field of bisphosphonates and osteoporosis. (D.I. 142 at 17-18; D.I. 141 at 41). The Court bases this finding on a combination of Merck and Teva's proffered interpretation of one skilled in the art and finds that there are no significant differences between the two proffered definitions.

ii. Scope and Content of Prior Art

At the outset, the Court notes that Merck has never disputed that it was known that once-weekly dosing would be efficacious in providing the alendronate sodium needed to inhibit bone resorption. (D.I. 145 at 15). However, Merck contends that it is the safety concern about high oral doses, specifically unit doses higher than 20 mg, that obscured the advantageous once-weekly invention for the management of osteoporosis. Id. Thus, the issue is when viewing the mosaic of the prior art, whether those of ordinary skill in the art would have had the motivation to formulate a once-weekly seven-fold daily dose of alendronate sodium, despite safety concerns.

The Court concludes that the history of bisphosphonates as a class is minimally relevant to the instant discussion because although alendronate is a bisphosphonate and general knowledge of

bisphosphonates is certainly within the knowledge of one of ordinary skill in the art during the relevant time period, it was also well known that each bisphosphonate had its own unique characteristics. (See DTX 547 at 543) (Dr. Papapoulos, Merck's expert, noting that because of differences in mechanisms of action and pharmacological and toxicological profiles, it is "important that specific properties of every individual bisphosphonate be determined and that results obtained with one bisphosphonate not be extrapolated readily to the whole class."). As a result, although the earlier bisphosphonates etidronate, clodronate and pamidronate had dose related gastrointestinal side effects, the Court concludes that this fact holds little weight in its obviousness analysis given the unique characteristics of each bisphosphonate, particularly with side effects. (Papapoulos at 653-654; Russell at 384-385; PTX 110 at 127, 129, 130; PTX 111 at 148, 149, 152; PTX 112 at 154, 15, 1585; PTX 113 at 170, 171, 175; PTX at 289, E91, C278, C279).

Therefore, the Court will focus its discussion on the prior art dealing with alendronate. The 1995, 1997, and 2000 editions of "Bisphosphonates in Bone Disease" written by Professor Herbert Fleish, who is described as the "father of bisphosphonates", reported that oral alendronate sodium can cause gastrointestinal disturbances at doses of 40 mg. (PTX 111 at 148; PTX 112 at 153; PTX 113 at 169; see also PTX 300 at 26). Further, in the 1997

and 2000 editions, Dr. Fleish reported that a 40 mg dose may cause gastrointestinal disturbances in patients with osteoporosis, but that the same dose was well tolerated in patients with Paget's disease. (PTX 112 at 153; PTX 113 at 169).

Additionally, the Court finds that case reports are probative in its obviousness inquiry because, as Dr. Fennerty testified, they often contain information that would alter the way a physician would treat patients. (Fennerty at 247-248). Case reports are publications usually involving one or a few patients that have an outcome of clinical relevance or importance. (Fennerty at 246-247). In October 1995, Maconi[6] published a case report in the American Journal of Gastroenterology, which reported that an osteoporosis patient after taking 5 mg of alendronate, had an endoscopy which revealed severe damage to the esophagus. (Fennerty at 249-250). Dr. Fennerty testified that this case report was significant because the particular journal it was published in was "clinically relevant" and because this "severity of injury had never been reported in a patient taking a bisphosphonate prior to this, especially a bisphosphonate that was being used now very commonly in clinical practice as it had just been released at about the time the case report was published." (Fennerty at 250). In October 1996, De Groen published an article in The New England

[6] Maconi, The American Journal of Gastroenterology, (1995) (PTX 90).

Journal of Medicine which set out three case reports describing the side effects of alendronate sodium. (PTX 91). The first case report reported that a 73-year-old woman developed chest pain and dysphagia after her first dose of 10 mg of alendronate sodium. (PTX 91 at 1016-1017). After two more doses she was transferred to the Mayo Clinic where an endoscopy revealed severe ulcerative esophagitis. (PTX 91 at 1017; Fennerty at 254-56). The other two case reports revealed that two additional women developed severe esophageal injury as a result of taking 10 mg oral dose of alendronate sodium. (PTX 91 at 1017; Fennerty 254-256). The article also revealed that Merck revised dosing instructions in the Fosamax product circular based on the results noted in the paper so as to further minimize potential for prolonged contact of the drug with the esophagus and thus, to reduce the risk of injury. (PTX 91 at 1020). Additional case reports published by Abdelmalek (PTX 96), Sorrentino (PTX 98), Naylor (PTX 101), Rimmer (PTX 102), Pizzanni (PTX 109) and Girelli (PTX 106) also suggested evidence that alendronate sodium may be associated with severe side effects not recognized in clinical trials. (Fennerty at 259).

The Court also finds that several studies dealing with alendronate are significant. In 1993, Harris[7] published an early Phase II study, which is a dose-ranging study used to determine

[7] Harris, Journal of Clinical Endocrinology and Metabolism, (1993) (PTX 116).

the dose and the preliminary data on both the safety and efficacy of a drug, sponsored by Merck in the Journal of Clinical Endocrinology and Metabolism investigating the effects of oral alendronate sodium treatment. (PTX 116; Russell at 159, 364-65). The women in this study were between the ages of 40 and 60 and did not have osteoporosis. The women were treated with alendronate sodium doses from 5 to 40 mg for six weeks and the dosages were well-tolerated. (PTX 116 at 1399).

Merck then sponsored a study investigating the effects of a range of different oral doses of alendronate for the treatment of osteoporosis. (PTX 69). The results of this study were published by Chestnut in 1995 in the American Journal of Medicine. The Chestnut study lasted for two years and involved 188 women with osteoporosis. (PTX 69; Yates at 502-504). Of these women, 31 were exposed to placebo, 32 to 5mg, 30 to 10 mg, 32 to 20 mg and 63 to 40 mg of alendronate sodium. (PTX 69 at Table 1). As of 1996, the Chestnut study was the only study that administered alendronate sodium to osteoporosis patients. (PTX 69; Markowitz at 478-479). Chestnut reported that nine women discontinued alendronate sodium therapy due to gastrointestinal side effects that included nausea, dyspepsia, mild esophagitis/gastritis and abdominal pain. (PTX 69 at 150; Markowitz at 479-482; Fennerty at 265-66). Nine women withdrew from treatment because of these side effects: seven women

withdrew from the 40 mg dose, one woman withdrew from the 20 mg dose and one women withdrew from the group taking between 5 and 10 mg doses. (PTX 69 at 150; Markowitz at 479-482; Fennerty at 266; Yates at 539-540). Chestnut also reported that the gastrointestinal side effects "occurred primarily in the first year during treatment with 40 mg alendronate." (PTX 69 at 150, col. 1). Dr. Fennerty testified that the fact that 11.1% (7 out of 63) withdrew from the 40 mg alendronate dose was noteworthy within the context of a clinical trial.[8]

Teva contends that the April and July 1996 editions of the Lunar News render claims 29 and 37 of the '329 Patent obvious. The July 1996 Lunar News issue contained a section entitled, "Update Bisphosphonate." (PTX 29 at 23). The section discusses bisphosphonates as a treatment for osteoporosis. Id. In reference to the use of alendronate for treatment of osteoporosis, it states that "[s]ome United States physicians are reluctant to treat because of: a) side effects; b) difficulty of dosing; and (c) high costs ($700/year)." (PTX 19 at 23). To

[8] The Court concludes that studies dealing with Paget's disease are not relevant to its analysis because it was well-known to those of ordinary skill in the art that patients with Paget's disease tolerate higher doses of alendronate than patients with osteoporosis. (Papapoulos at 710-711; PTX 112 at 153; PTX 113 at 169; see also PTX 300 at 26). Thus, the Court finds that tolerability of alendronate sodium from studies involving Paget's patients should not be extrapolated to a discussion of osteoporosis about the tolerability of alendronate. For this reason, the Court will not address studies dealing with Paget's disease and the tolerability of higher doses of alendronate sodium.

address the difficulty of dosing and high costs the article suggested:

> The difficulties with oral bisphosphonates may favor their episodic (once/week) or cyclical(one week each month)administration. Even oral alendronate potentially could be given in a 40 or 80 mg dose once/week to avoid dosing problems and reduce costs.

PTX 29 at 23. In a section entitled "Update: Bisphosphonates," the April 1996 edition of the Lunar News discusses difficulties of the dosing regimen associated with alendronate and states:

> one of the difficulties with alendronate is its low oral bioavailability. When taken with water in a fasting state, only about 0.8% of the oral dose is bioavailable. Even coffee or juice reduces this by 60%, and a meal reduces it by > 85%. Alendronate must be taken, after an overnight fast, 30-60 minutes before breakfast. Subjects should remain seated or standing; a very small group of patients have reported some upper gastrointestinal distress if this is not done. This regime may be difficult for the elderly maintain chronically. An intermittent treatment program (for example, once per week, or one week every three months), with higher oral dosing, needs to be tested.

DTX 417 at 31. (citations omitted).

iii. Differences Between the Prior Art and the Claims at Issue

The Court concludes that the prior art cited above demonstrates that the suggestion to give 40 or 80 mg of alendronate sodium to treat or prevent osteoporosis was not clinically useful or obvious in July 1997 because of the known dose-related gastrointestinal side effects. Further, the Court is not persuaded that the two Lunar News articles, not published

in peer-reviewed journals or authored by one skilled in the art, either alone or in combination, overcame the serious side effect concerns associated with higher dosage units of alendronate sodium. For example, Dr. Fennerty, whom the Court finds very credible, testified that in light of the prior art, any physician would have been "extraordinarily concerned" to suggest a 40 or 80 mg dose because alendronate sodium was a new compound that had been associated with dose-related injury and severe injuries in case reports. (Fennerty at 270-271; see also PTX 69, 91, PTX 300 at 14). In this regard Dr. Fennerty testified:

> Q: Now in July of '97 or any period preceding that, what would your opinion be about a suggestion that you give 40 or 80 milligrams of alendronate to an osteoporotic woman?
> A. Given what I just described, a new compound, a Dear [D]octor letter , publications in the New England Journal of severe caustic injury, smattering case reports around that, the Chestnut [sic] paper before talking about as you go up on a dose, that you may be seeing more adverse effects, the smattering of papers, and now animal data showing that types of patients that use NSAIDS use some higher dose of these compounds, shows evidence of gastric injury in the model, I would have been extraordinarily concerned about anybody suggesting that this was a useful clinical approach at that point and time.

(Fennerty at 270-21). Additionally, Dr. Papapoulous testified about the concerns of side effects associated with the suggestion in the July 1996 Lunar News where he stated, "[Lunar News] is using 40 and 80 not on any scientific rationale, but because it is available. Secondly, he doesn't tell us how he's going to address the issue of side effects, which is one of the main

points in this particular article." Papapoulos at 665-666. Thus, in light of the case reports, and the Chestnut study, in conjunction with observations written about alendronate by Dr. Fleish, the Court concludes that the Lunar News references did not render the seven-fold daily dose of alendronate for the treatment and prevention of osteoporosis obvious given the clearly documented and known dose related gastrointestinal side effects associated with high doses (over 20 mg) of oral alendronate.

First, the April 1997 Lunar News did not deal with the specific dosages of 70 or 35 mg in relation to its discussion of once-weekly dosing of alendronate. Second, the July 1996 Lunar News listed 40 and 80 as compared to 70 and 35 mg dosages as suggested by the '329 Patent and did not deal with the problem of known gastrointestinal side effects. Additionally, in reaching its conclusion, the Court gives more weight to the prior art references written and reviewed by those skilled in the art such as the Chestnut study and the De Groen case report as opposed to the Lunar News, a quarterly newsletter written by someone without a Ph.D. or MD. in the applicable field.

iv. Secondary Indicia of Non-Obviousness

As for the secondary considerations of non-obviousness, the Court finds that Merck has presented sufficient evidence to show that the 35 mg and 70 mg once-weekly dosing of Fosamax was

commercially successful. On this issue, the Court finds Dr. Vellturo's testimony persuasive. Dr. Vellturo testified regarding the evidence of increased sales after the launch of once-weekly Fosamax.

Originally, Merck's Fosamax osteoporosis product line consisted of once-daily 10 and 5 mg Fosamax tablets. (D.I. 138 at 32). Dr. Vellturo testified that daily Fosamax was a successful product that enjoyed an average increase in sales of 152 million dollars per year for each of the four years preceding the introduction of the once-weekly Fosamax. (Vellturo at 718-720; PTX 166; PTX 300 at 37). In 2001, the first full year following the launch of the once-weekly dosing regimen, the sales increase was 343 million dollars, more than double the expected increase, without any corresponding relative increase in expenditures. (Vellturo at 719-720; PTX 166; PTX 300 at 37).

The Court finds that further evidence of the success of the once-weekly dosing regimen is present in the prescription data for the Fosamax tablets. A sharp increase in physician adoption of Fosamax upon the introduction of the once-weekly dosing regimen is manifested in the number of total prescriptions reported each month for Fosamax. (Vellturo at 723; PTX 164; PTX 300 at 32, 33, 36). The marked increase in prescription volume of once weekly dosages of Fosamax tablets is more compelling in light of its effects on the osteoporosis market in general. FAME

is an acronym for the four prescription drug products whose primary indication is for the treatment of osteoporosis, (i.e., Fosamax, Actonel, Miacalcin, and Evista). (Vellturo at 722, 753-754). IMS is a data collection firm specializing in data reflecting the prescribing patterns of physicians and in prescription volume data. (Vellturo at 716-717). Within six months of its launch, once-weekly Fosamax tablets became the most prescribed drug in the FAME market. (PTX 164; PTX 165; PTX 300 at 33). Based on the IMS data points present in the plot of monthly total prescriptions, it can be calculated that the Fosamax franchise share of the FAME market grew from 45 % to 55 % in the first six months after the introduction of the once-weekly dosing regimen. (PTX 164; PTX 300 at 33).

Teva's expert Dr. Rozek testified that the increase in Fosamax sales could be due to other factors such as the increasing number of Americans over the age of sixty, the increasing awareness of osteoporosis, an increase in the number of people seeking treatment for osteoporosis and Merck's marketing efforts. However, the Court finds Dr. Rozek's explanation unpersuasive because he offered no affirmative opinion as to what affect these factors would have on the analysis of the FAME market as a whole or with Fosamax individually. (Rozek at 871-72; 869; 878). In fact, Dr. Rozek testified the he was "not instructed to do anything affirmative

with regard to the measuring of any relationship that might exist between the ['329 Patent] and sales, or success of Fosamax." (Rozek at 869). In the Court's view, Dr. Rozek's suggestion that there are factors that Dr. Vellturo should have considered, is not sufficient to rebut the affirmative evidence of the commercial success of the once-weekly dosing regimen. (Rozek at 878-79). Also, the Court concludes that Merck has shown a sufficient nexus between the claimed secondary considerations and the patented method given the testimony of Dr. Vellturo and the timing of the launch of the once-weekly dosing regimen for Fosamax. Accordingly, the Court has given the above discussed secondary considerations the importance they deserve in reaching its conclusion of nonobviousness. See Minnesota Mining & Manufacturing Co. v. Johnson & Johnson Orthopedics, Inc. 976 F.2d 1559, 1573 (Fed. Cir. 1992) (noting the importance of secondary considerations in the obviousness analysis).

v. Summary

In sum, the Court concludes that Teva has not proven by clear and convincing evidence that it was obvious to combine the Lunar News suggestions in light of the knowledge of one of ordinary skill in the art of the gastrointestinal side effects accompanying large doses of oral alendronate. In addition, the Court finds that the significant secondary considerations offered by Merck undermine any claim of obviousness, and accordingly, the

Court concludes that Teva has not proven by clear and convincing evidence that the '329 Patent was obvious in light of prior art.

V. Unenforceability Due To Inequitable Conduct

A. The Inequitable Conduct Standard

As a general matter, patent applicants and their patent attorneys have a duty of candor, good faith and honesty in their dealings with the PTO. 37 C.F.R. § 1.56(a). The duty of candor, good faith and honesty includes the duty to submit truthful information and the duty to disclose to the PTO information known to the patent applicants or their attorneys which is material to the examination of the patent application. Elk Corp. of Dallas v. GAF Bldg. Materials Corp., 168 F.3d 28, 30 (Fed. Cir. 1999). Breach of the duty of candor, good faith and honesty may constitute inequitable conduct. Id. If it is established that a patent applicant engaged in inequitable conduct before the PTO, the entire patent application so procured is rendered unenforceable. Kingsdown Medical Consultants v. Hollister Incorporated, 863 F.2d 867, 877 (Fed. Cir. 1988).

A patent applicant engages in inequitable conduct before the PTO when he withholds or misrepresents information material to the patentability of his invention, with an intent to deceive. See Nobelpharma AB v. Implant Innovations, Inc., 141 F.3d 1059, 1064 (Fed. Cir. 1998); (citing Molins PLC v. Textron, Inc., 48 F.3d 1172, 1178 (Fed. Cir. 1995)). Inequitable conduct

encompasses affirmative misrepresentations of material fact, failure to disclose material information, or submission of false material information, coupled with an intent to deceive. Baxter Int'l, Inc. v. McGaw Inc., 149 F.3d 1321, 1327 (Fed. Cir. 1998) (citing Nobelpharma, 141 F.3d at 1068-71). In order to establish unenforceability based on inequitable conduct, Teva must prove, by clear and convincing evidence, that material information was intentionally withheld for the purpose of misleading or deceiving the patent examiner. See Allied Colloids, Inc. v. American Cyanamid Co., 64 F.3d 1570, 1578 (Fed. Cir. 1995) (citation omitted).

A determination of inequitable conduct entails a two step analysis. First, the court must determine whether the withheld information meets a threshold level of materiality. A reference is considered material if there is a substantial likelihood that a reasonable examiner would consider it important in deciding whether to allow the application to issue as a patent. See id. This determination is not the end of the inquiry with respect to intent. The Federal Circuit has stated that, "materiality does not presume intent, which is a separate and essential component of inequitable conduct." See Manville Sales Corp. v. Paramount Sys., Inc., 917 F.2d 544, 552 (Fed. Cir. 1990) (internal citation omitted).

After determining if the applicant withheld information that is material, the court must then determine whether the evidence demonstrates a threshold level of intent to mislead the PTO. See Baxter, 149 F.3d at 1327. "Intent to deceive cannot be inferred solely from the fact that information was not disclosed; there must be a factual basis for a finding of deceptive intent." Hebert v. Lisle Corp., 99 F.3d 1109, 1116 (Fed. Cir. 1996). Therefore, in order to satisfy the intent to deceive element of inequitable conduct, the conduct when viewed in light of all of the evidence, including evidence of good faith, must demonstrate sufficient culpability to require a finding of intent to deceive. See Paragon Podiatry Lab., Inc. v. KLM Lab, Inc., 984 F.2d 1182, 1189 (Fed. Cir. 1993).

The initial determinations of materiality and intent to deceive are questions of fact. See Monon Corp. v. Stoughton Trailers, Inc., 239 F.3d 1253, 1261 (Fed. Cir. 2001) (citation omitted). Once these facts are established, the court should then weigh the findings and their premises and determine, in its discretion, whether to hold the patent unenforceable. See ATD Corp. v. Lydall, Inc., 159 F.3d 534, 547 (Fed. Cir. 1998).

B. Whether Dr. Yates Engaged In Inequitable Conduct Before the PTO Rendering The '329 Patent Unenforceable

Teva contends that Dr. Yates engaged in inequitable conduct before the PTO rendering the '329 Patent unenforceable.

Specifically, Teva contends that Dr. Yates intentionally withheld the July 1996 edition of the Lunar News from the Patent Examiner.

In response, Merck contends that the July 1996 Lunar News was not considered material because it was cumulative to the cited prior art. Merck further contends that Dr. Yates did not make any material misrepresentations to the PTO, and that Teva cannot establish an intent to deceive the PTO by clear and convincing evidence.

1. The Allegedly Withheld Prior Art

In the Court's view, the July 1996 Lunar News has some degree of materiality because it has relevance to the claimed invention, specifically, the recommended once-weekly dosage level of alendronate for osteoporosis patients. Additionally, the Court finds that it is not cumulative to the cited prior art, specifically the April 1997 Lunar News because, although the April edition mentions a 40 mg dose of alendronate it does not suggest a 40 or 80 mg dose in the context of once-weekly dosing as the July 1996 edition of the Lunar News does. However, as previously discussed, the Court finds that the July 1996 Lunar News does not reflect the claimed invention directly and does not render the claimed invention invalid as either obvious or anticipated. See, e.g., Life Technologies, Inc. v. Clontech Labs. Inc., 224 F.3d 1320, 1325 (Fed. Cir. 2000) (citing 35 U.S.C. § 103(a) and stating that "the path that leads an inventor

to the invention is expressly made irrelevant to patentability by statute").

2. Intent to Deceive

The Court concludes that Teva has failed to meet its burden of demonstrating a prima facie showing of intent to deceive the PTO. As to this issue, Teva contends that Dr. Yates' testimony indicating that he did not read the July 1996 Lunar News was not credible in light of the fact that in September 1996, Dr. Yates received a memorandum discussing Lunar News' comments about alendronate, with the relevant portions of the July issue attached. Further, Teva argues that Dr. Yates' testimony that he did not focus on the July 1996 issue again on May 21, 1997 at a meeting with Lunar Corp., where the July 1997 issue was attached as an agenda item, is not credible.

The Court finds that this evidence of intent to deceive falls short of the applicable standard. Dr. Yates testified unequivocally that he had never seen the statements regarding once-weekly dosing of alendronate in the July 1996 Lunar News prior to this litigation. (Yates at 533-34; 572-573; 575). Additionally, in reference to the September 1996 memo that was circulated with the July 1996 Lunar News as an attachment, the Court recognizes that there were twelve pages attached to the original memo and the relevant article in the July 1996 Lunar News was the last page. Based on this, the Court finds Dr.

Yates' testimony that he did not read the July 1996 Lunar News article in September 1996, credible. Likewise, the Court does not find Teva's assertion that Dr. Yates should have read the article that was attached to the agenda at the May 1997 meeting, probative of Dr. Yates' intent to deceive because attendees, including Dr. Mazess, did not recall whether the once-weekly dosing concept was specifically addressed at the meeting. (Mazess Dep. at 180:19-181:7; Beckman Dep. at 131:1-23; Magri Dep. at 105:7-25; Sherwood Dep. at 146:17-23, 147:11-148:3). Further, the Court finds that even if once-weekly dosing was discussed at the meeting, the focus of the discussion was more likely than not centered on the April 1997 edition of the Lunar News, which was disclosed to the examiner, rather than the July 1996 edition because the April 1997 edition came out in the month preceding the meeting.

"In a case involving an omission of a material reference to the PTO, there must be clear and convincing evidence that the applicant made a deliberate decision to withhold a known reference." Baxter Int'l, Inc. v. McGaw, Inc., 149 F.3d 1321, 1329 (Fed. Cir. 1998). The Court concludes that Teva has proffered insufficient evidence of an intent to deceive on the part of Dr. Yates. Accordingly, the Court cannot conclude that Dr. Yates engaged in inequitable conduct before the PTO by failing to disclose material prior art.

Conclusion

For the reasons discussed, the Court concludes that Teva has not proven that the patent-in-suit is invalid or that Merck engaged in inequitable conduct before the PTO.

An appropriate Order will be entered.

IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

MERCK & CO., INC.	:	
	:	
Plaintiff,	:	
	:	
v.	:	Civil Action No. 01-048-JJF
	:	(Consolidated)
TEVA PHARMACEUTICALS, INC.	:	
	:	
Defendant.	:	

ORDER

NOW THEREFORE, For The Reasons discussed in the Opinion issued this date, IT IS HEREBY ORDERED this 28th day of August 2003 that:

1) Defendant's Motion to Preclude Plaintiff Merck from Relitigating the Factual Findings Underlying the Decision in Teva Pharmaceuticals Ltd. et al. Instituto Gentili Spa et al. (D.I. 113) is **DENIED**.

2) Plaintiff shall submit a Proposed Order within ten (10) days of its receipt of this Memorandum Opinion. Defendant may stipulate to Plaintiff's Proposed Order, or file any objections within ten (10) days of their receipt of the Proposed Order.

JOSEPH J. FARNAN, JR.
UNITED STATES DISTRICT JUDGE